Invited Editorial

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ESSENTIAL HYPERTENSION: IS IT ALL IN THE BRAIN?

After a century of work on high blood pressure, do we understand it? In part, yes. Most of us agree—as a prejudiced observer I would rather say, admit—that essential hypertension mainly derives from the brain. In their Lead Article, **Julian Paton** and **Mohan Raizada** concentrate on the rat. Why does an animal model of hypertension created by selective inbreeding seem to have especially involved the brain's blood supply? The arteries of the brainstem in spontaneous hypertensive rats (SHRs; developed by Aoki and Okamoto) are much smaller than those in the Wistar-Kyoto rats from which SHRs were derived. The arterial endothelium in SHRs appears to be unduly sticky. It encourages dense leukocyte adhesion that may restrict blood flow and compromise oxygen delivery to important nuclei. These include the nuclei of the solitary tracts, which (in humans) lie in the floor of the 4th ventricle at the level of the obex. There, they receive afferent nerve impulses from the arterial baroreceptors and connect with inhibitory caudal medullary nuclei. The latter have connections with rostral ventrolateral medullary nuclei whose activity increases when inhibition is withdrawn. A comparable complicated reciprocal system presumably underlies the human "baroreflex" relating arterial pressure inversely to heart rate.

The invited Discussants of our Dialogue concur that essential hypertension is initiated and sustained by the sympathetic nervous system. **Murray Esler** and **Elisabeth Lambert** demonstrate that fat and thin essential hypertensive individuals have different patterns of sympathetic nervous system activity, which need to be taken into account when deciding on treatment. **Guido Grassi** pays special attention to increased insulin resistance, which may accompany, and perhaps cause, increased sympathetic nervous system activity: or is it the other way around? **Vito Campese** and his colleagues suggest that in chronic renal failure, afferent nerve impulses from injured kidneys may activate the sympathetic nervous system and raise blood pressure.

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I am delighted that Patrice Guyenet regards as seminal Harvey Cushing's century-old paper quantifying the relation between brainstem compression and the resultant blood pressure elevation, and that the work has a "considerable following." Arthur Guyton recognized the "Cushing response" as immensely powerful, but he regarded it only as a "last ditch" protection for an ischemic brain. But Patrice is also the co-author of a chapter in a 1985 book that emphasized the "critical importance of employing conscious unrestrained animals in studies of cardiovascular regulation."[1] General anesthesia makes all the difference, as Jim McCubbin and I showed in Cleveland 45 years ago.[2] Also, in unanesthetized fetal sheep in utero, blood pressure accurately follows induced elevations of cerebrospinal fluid (CSF) pressure.[3] There have been relevant human observations, eg, a 33-year-old woman unconscious from a subarachnoid hemorrhage in whom each repeated spontaneous elevation in CSF pressure produced an exactly corresponding elevation in blood pressure 20 seconds later.[4]

So do I think that essential hypertensives get cerebral ischemia? Yes I do—but only in a restricted sense. When any of us rest or sleep and our blood pressure falls to a basal level, I have suggested that any further fall is arrested as soon as the brainstem detects the approach of unfavorable perfusion conditions.[5] Basal elevations of blood pressure determine the pattern of blood pressure behavior later in the day, as a superb Japanese community-based study showed.[6]

Kety and his colleagues found that cerebral blood flow was normal in essential hypertension.[7] But a few weeks after one kidney has been removed from a dog and stable hypertension has been established by inducing perinephritis or by using a constricting Goldblatt clamp on the main renal artery, renal blood flow returns to its original level even though the hypertension persists.[8-10] So the normality of cerebral blood flow in essential hypertension is not a good reason to reject increased proximal cerebral arterial resistance as a cause of raised blood pressure. Unless you have examined the main cerebral arteries in the neck and skull base of nearly 100 human cadavers (as Drew Thomson and I did long ago[11,12]), you may not appreciate the extent to which these large arteries can be narrowed or even occluded by atheromatous deposits.

Although my interpretation of the etiology of essential hypertension is fiercely disputed, it has two merits. It explains why there is no natural animal model for essential hypertension, apart from models involving the use of selective inbreeding or cholesterol feeding. And invoking a structural etiology also explains why prolonged (6-year) hypotensive drug treatment of essential hypertensives in a large study had no lasting effect on blood pressure, which reverted to its original value soon after the drug treatment was withdrawn.[13] Should we perhaps pay as much attention to preventing or reversing the stenotic atheromatous disease of our patients' large cerebral arteries as we do to lowering their blood pressure with drugs?

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